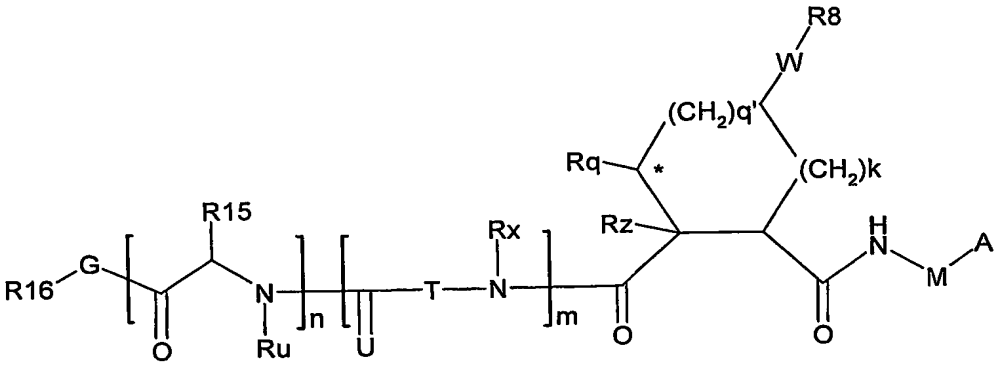
Claims

1. A compound of the formula VI:



VI

wherein

A is $C(=O)OR^1$, $C(=O)NHSO_2R^2$, $C(=O)NHR^3$, or $CR^4R^{4'}$ wherein;

R^1 is hydrogen, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^2 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^3 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, -OC_1-C_6alkyl, -OC_0-C_3alkylcarbocyclyl, -OC_0-C_3alkylheterocyclyl;

R^4 is halo, amino, or OH; or R^4 and $R^{4'}$ together are =O;

$R^{4'}$ is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

wherein R^2, R^3, and $R^{4'}$ are each optionally substituted from 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, $NH_2C(=O)$-, Y-NRaRb, Y-O-R_b, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)Orb and Y-NRaC(=O)ORb;

Y is independently a bond or C_1-C_3alkylene;

Ra is independently H or C_1-C_3alkyl;

Rb is independently H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl or C_0-C_3alkylheterocyclyl;

p is independently 1 or 2;

M is $CR^7R^{7'}$ or NRu;

Ru is H or C_1-C_3alkyl;

R^7 is C_1-C_6alkyl, C_0-C_3alkylC_3-C_7cycloalkyl, or C_2-C_6alkenyl, any of which is optionally substituted with 1-3 halo atoms, or an amino, –SH or C_0-C_3alkylcycloalkyl group; or R^7 is J;

$R^{7'}$ is H or taken together with R^7 forms a C_3-C_6cycloalkyl ring optionally substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is C_1-C_6alkyl, C_3-C_5cycloalkyl, C_2-C_6alkenyl any of which may be optionally substituted with halo; or $R^{7'a}$ is J;

q' is 0 or 1 and k is 0 to 3;

Rz is H, or together with the asterisked carbon forms an olefinic bond;

Rq is H or C_1-C_6alkyl;

W is -CH_2-, -O-, -OC(=O)H-, -OC(=O)-, -S-, –NH-, -NRa, -$NHSO_2$-, -NHC(=O)NH- or -NHC(=O)-, -NHC(=S)NH- or a bond;

R^8 is a ring system containing 1 or 2 saturated, partially saturated or unsaturated rings each of which has 4-7 ring atoms and each of which has 0 to 4 hetero atoms selected from S, O and N, the ring system being optionally spaced from W by a C_1-C_3alkyl group; or R^8 is C_1-C_6alkyl; any of which R^8 groups can be optionally mono, di, or tri substituted with R^9, wherein

R^9 is independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, $NH_2C(=O)$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb and Y-NRaC(=O)ORb; wherein said carbocyclyl or heterocyclyl moeity is optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino, sulfonyl, (C_1-C_3 alkyl)sulfonyl, NO_2, OH, SH, halo, haloalkyl, carboxyl, amido;

Rx is H or C_1-C_5 alkyl; or Rx is J;

T is -CHR^{11}- or -NRd-, where Rd is H, C_1-C_3alkyl or Rd is J;

R^{11} is H or R^{11} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-

NRaC(=O)Rb, Y-NHSO$_p$Rb, Y-S(=O)$_p$Rb, Y-S(=O)$_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb; or R^{11} is J;

J, if present, is a single 3 to 10-membered saturated or partially unsaturated alkylene chain extending from the R^7/$R^{7'}$ cycloalkyl, or from the carbon atom to which R^7 is attached to one of Rd, Rj, Rx, Ry or R^{11} to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -NR^{12}-,and wherein 0 to 3 carbon atoms in the chain are optionally substituted with R^{14}; wherein;

R^{12} is H, C_1-C_6 alkyl, C_3-C_6cycloalkyl, or COR^{13};

R^{13} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^{14} is independently selected from H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, hydroxy, halo, amino, oxo, thio, or C_1-C_6 thioalkyl;

m is 0 or 1; n is 0 or 1;

U is O or is absent;

R^{15} is H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1-C_6 alkyl, C_0-C_3alkylheterocyclyl, C_0-C_3alkylcarbocyclyl, $NH_2C(=O)$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO$_p$Rb, Y-S(=O)$_p$Rb, Y-S(=O)$_p$NRaRb, Y-C(=O)ORb and Y-NRaC(=O)ORb;

G is -O-, -NRy-, -NRjNRj-;

Ry is H, C_1-C_3 alkyl; or Ry is J;

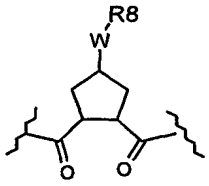
one Rj is H and the other Rj is H or J;

R^{16} is H; or R^{16} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO$_p$Rb, Y-S(=O)$_p$Rb, Y-S(=O)$_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

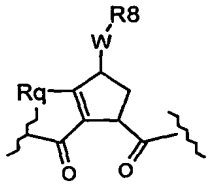
or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1, where M is $CR^7R^{7'}$.

3. A compound according to claim 1, with the partial structure:



4. A compound according to claim 1, with the partial structure



5. A compound according to claim 4, wherein Rq is C_1-C_3 alkyl, preferably methyl.

6. A compound according to claim 1, wherein m is 0 and n is 0.

7. A compound according to claim 6, wherein G is –NRy- or –NRjNRj-.

8. A compound according to claim 7, where Ry or one of the Rj groups is J, thereby defining a macrocyclic compound.

9. A compound according to claim 7, wherein R^{16} is H, C_1-C_6alkyl or C_3-C_6 cycloalkyl.

10. A compound according to claim 1, wherein m is 1.

11. A compound according to claim 10, wherein U is O.

12. A compound according to claim 10, wherein T is CR^{11}.

13. A compound according to claim 12, wherein R^{11} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylaryl or C_0-C_3alkylheteroaryl, any of which is optionally

substituted with halo, amino, C_1-C_6alkoxy, C_1-C_6thioalkyl, $COOR^{14}$, carboxyl, (C_1-C_6alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl; or especially substituted with hydroxyl or $COOR^{14}$.

14. A compound according to claim 13, wherein R^{11} is tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimetyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl, especially tert-butyl, iso-butyl, or cyclohexyl.

15. A compound according to claim 10, wherein one of Rd, Rx or R^{11} is J, thereby defining a macrocyclic compound.

16. A compound according to claim 10, wherein n is 1.

17. A compound according to claim 16, wherein R^{15} is C_1-C_6alkyl or C_0-C_3alkylcarbocyclyl, either of which is optionally substituted.

18. A compound according to claim 17, wherein R^{15} is cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.

19. A compound according to claim 10, wherein G is NRy or NRjNRj, where Ry or one Rj is H or methyl and the other is H.

20. A compound according to claim 19, wherein R^{16} is H, C_1-C_6alkyl or a 5 or 6 membered heterocycle, especially morpholine, piperidine or piperazine.

21. A compound according to claim 10, wherein R^{16} is C_1-C_6alkyl, C_0-C_3alkylheterocyclyl, C_0-C_3alkylcarbocyclyl, any of which is optionally substituted with hydroxy, halo, amino, or C_1-C_6alkoxy.

22. A compound according to claim 21, wherein R^{16} is 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

23. A compound according to claim 1, wherein W is -OC(=O)-, -NRa-, -$NHS(O)_2$-or -NHC(=O)-; or especially –OC(=O)NH- or –NH.

24. A compound according to claim 1, wherein W is –S-, a bond or especially –O-.

25. A compound according to claim 23 or 24 wherein R^8 is optionally substituted C_0-C_3alkylcarbocyclyl or optionally substituted C_o-C_3-alkylheterocyclyl.

26. A compound according to claim 25, wherein the C_0-C_3 alkyl moiety is methylene or preferably a bond.

27 A compound according to claim 26 wherein R^8 is C_0-C_3alkylaryl, or C_0-C_3alkylheteroaryl, either of which is optionally mono, di, or tri substituted with R^9, wherein;
R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, NO_2, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C_1-C_6alkyl, C_0-C_3alkylaryl, C_o-C_3alkylheteroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R^{10}; wherein
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, C_1-C_3 alkyl amide, sulfonylC_1-C_3alkyl, NO_2, OH, halo, trifluoromethyl, carboxyl, or heteroaryl.

28. A compound according to claim 27 wherein R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, amino, di-(C_1-C_3 alkyl)amino, C_1-C_3alkylamide, aryl or heteroaryl, the aryl or heteroaryl being optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino, mono- or di-C_1-C_3 alkylamino, amido, C_1-C_3 alkylamide, halo, trifluoromethyl, or heteroaryl.

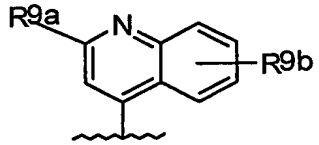
29. A compound according to claim 28, wherein, R^{10} is C_1-C_6alkyl, C_1-C_6alkoxy, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3-alkylamide, halo, or heteroaryl.

30. A compound according to claim 29 wherein R^{10} is methyl, ethyl, isopropyl , tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3alkylamide, or C_1-C_3alkyl thiazolyl.

31 A compound according to claim 26, wherein R^8 is 1-naphthylmethyl, 2-naphthylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

32 A compound according to claim 31 wherein R^8 is 1-naphthylmethyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

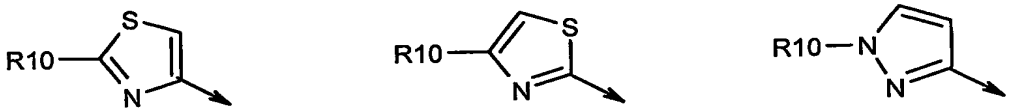
33 A compound according to claim 32 wherein R^8 is:



wherein R^{9a} is C_1-C_6 alkyl; C_1-C_6alkoxy; thioC_1-C_3alkyl; amino optionally substituted with C_1-C_6alkyl; C_0-C_3alkylaryl; or C_0-C_3alkylheteroaryl, C_0-C_3alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with R^{10} wherein R^{10} is C_1-C_6alkyl, C_0-C_3alkylC_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, C_1-C_3alkyl amide; and
R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3alkyl)amino, (C_1-C_3alkyl) amide, NO_2, OH, halo, trifluoromethyl, carboxyl.

34 A compound according to claim 33, wherein R^{9a} is aryl or heteroaryl, either of which is optionally substituted with R^{10} as defined.

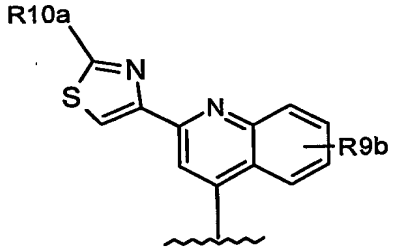
35 A compound according to 34, wherein R^{9a} is selected from the group consisted of:



wherein R^{10} is H, C_1-C_6alkyl, or C_0-C_3alkylcycloalkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3alkyl)amide.

36. A compound according to claim 34, wherein R^{9a} is optionally substituted phenyl, preferably phenyl substituted with C_1-C_6alkyl; C_1-C_6alkoxy; or halo.

37. A compound according to claim 33, wherein R^8 is:



wherein R^{10a} is H, C_1-C_6alkyl, or C_0-C_3alkylcarbocyclyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3 alkyl)amide, heteroaryl or heterocyclyl; and R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3 alkyl)amino, (C_1-C_3 alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl.

38. A compound according to any claim 33, wherein R^{9b} is C_1-C_6-alkoxy, preferably methoxy.

39. A compound according to claim 1, wherein A is $C(=O)NHSO_2R^2$.

40. A compound according to claim 39, wherein R^2 is optionally substituted C_1-C_6 alkyl, preferably methyl.

41. A compound according to claim 39, wherein R^2 is optionally substituted C_3-C_7cycloalkyl, preferably cyclopropyl.

42. A compound according to claim 39, wherein R^2 is optionally substituted C_0-C_6alkylaryl, preferably optionally substituted phenyl.

43. A compound according to claim 1, wherein A is $C(=O)OR^1$.

44. A compound according to claim 43, wherein R^1 is H or C_1-C_6 alkyl, preferably hydrogen, methyl, ethyl, or tert-butyl.

45. A compound according to claim 2, wherein $R^{7'}$ is H and R^7 is n-ethyl, cyclopropylmethyl, cyclobutylmethyl or mercaptomethyl, preferably n-propyl or 2,2-difluoroethyl.

46. A compound according to claim 2, wherein R^7 and $R^{7'}$ together define a spiro-cyclopropyl or spiro-cyclobutyl ring, both optionally mono or di-substituted with $R^{7'a}$ wherein;
$R^{7'a}$ is C_1-C_6 alkyl, C_3-C_5cycloalkyl, or C_2-C_6 alkenyl, any of which is optionally substituted with halo; or R^{7a} is J.

47. A compound according to claim 47 wherein the ring is a spiro-cyclopropyl ring substituted with $R^{7'a}$ wherein;
$R^{7'a}$ is ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl.

48. A compound according to claim 2, wherein R^7 is J and $R^{7'}$ is H.

49. A compound according to claim 1, wherein J is a 3 to 8-membered saturated or unsaturated alkylene chain optionally containing one to two heteroatoms independently selected from: -O-, -S- or -NR^{12}- , wherein R^{12} is H, C_1-C_6 alkyl, such as methyl, or -C(=O)C_1-C_6 alkyl, such as acetyl.

50. A compound according to claim 49, wherein J is a 4 to 7-membered saturated or unsaturated, all carbon alkylene chain.

51. A compound according to claim 49, wherein J is saturated or mono-unsaturated.

52. A compound according to claim 49, wherein J is dimensioned to provide a macrocycle of 14 or 15 ring atoms.

53. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

54. A pharmaceutical composition according to claim 53, further comprising an additional HCV antiviral, selected from nucleoside analogue polymerase inhibitors, protease inhibitors, ribavirin and interferon.

55. Use of a compound as defined in claim 1 in therapy.

56. Use of a compound as defined in claim 1 in the manufacture of a medicament for the prophylaxis or treatment of flavivirus infections, including HCV.

57. A method for treatment or prophylaxis of flavivirus infection such as HCV comprising the administration of an effective amount of a compound as defined in claim 1 to an individual afflicted or at risk of such infection.